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Complete List of Authors:	Soumagne, Thibaud; Institut universitaire de cardiologie et de pneumologie de Quebec Guibert, Nicolas; Centre Hospitalier Universitaire de Toulouse, Service de pneumologie Atallah, Ihab; CHU Grenoble Alpes, Clinique universitaire d'ORL Lacasse, Yves; Institut universitaire de cardiologie et de pneumologie de Quebec Dutau, Hervé; Assistance Publique Hopitaux de Marseille Fortin, Marc; Institut universitaire de cardiologie et de pneumologie de Quebec
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Dilation versus laser resection in simple benign tracheal stenosis: protocol for a prospective international multicentre randomized controlled trial (AERATE trial)

Thibaud Soumagne[1], Nicolas Guibert[2], Ihab Atallah[3], Yves Lacasse[1], Hervé Dutau[4], Marc Fortin[1]

[1] Service de pneumologie, Institut universitaire de cardiologie et de pneumologie de Québec et Université Laval, Québec, Canada

[2] Service de pneumologie, Hôpital Larrey, Université Paul-Sabatier, Centre Hospitalier Universitaire de Toulouse, Toulouse, France.

[3] Clinique universitaire d'ORL, Centre Hospitalier Universitaire Grenoble-Alpes, Grenoble, France

[4] Service d'oncologie thoracique, maladie de la plèvre et pneumologie interventionnelle, hôpital Nord, Assistance publique-hôpitaux de Marseille, Marseille, France.

Corresponding author:

Thibaud Soumagne, MD, PhD

Service de pneumologie, Institut universitaire de cardiologie et de pneumologie de Québec et Université Laval, Québec, Canada

Email : thibaud_soumagne@live.fr

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ABTRACT

Introduction: Simple benign tracheal stenosis (SBTS) is a rare condition that results from progressive narrowing of the upper airways. Outcomes and treatment options depend on the benign or complex nature of the stenosis. Treatment options for SBTS include surgery and endoscopic techniques. The main endoscopic techniques used are dilation and laser resection. Observational and retrospective studies suggest that endoscopic laser resection may be more effective than dilation. We therefore aimed to compare the effectiveness of dilation and laser resection in preventing recurrence of SBTS.

Methods and analysis: AERATE is a multicentre, investigator-initiated, randomised controlled trial, comparing endoscopic dilation to endoscopic laser resection for SBTS (less than 1cm long without underlying cartilaginous damage) referred for endoscopic treatment (first treatment or recurrence). The study will be conducted in 3 centres in France and one in Canada with other centres from France and Canada expected to join. The primary outcome is the recurrence rate of stenosis at 2 years. Recurrence is defined as having a new onset of symptoms along with a stenosis of more than 40% (confirmed by endoscopy) requiring a new procedure. A sample size of 100 patients is calculated for the primary endpoint assuming a 10% recurrence rate in the laser resection group and 33% in the dilation group with a statistical significance level of 5%, a power of 80%.

Ethics and dissemination: This study is approved by local and national ethics committees as required. Results will be published, and trial data will be made available.

Trial registration: ClinicalTrials.gov: NCT04719845

Keywords: subglottic tracheal stenosis, dilation, laser resection, recurrence

Strengths and limitations of this study

- This is the first randomized controlled trial comparing endoscopic procedures in SBTS and is in fact the first randomized controlled trial in the field of SBTS to our knowledge.

- The primary endpoint is symptomatic endoscopically confirmed recurrence rate at 2 years which is an objective clinical endpoint. This outcome will allow us to provide a definitive answer to an important clinical question: “What is the most effective endoscopic technique to treat TS?”

- Adequate statistical power however relies on sufficient recruitment which can be a challenge in rare disease.

INTRODUCTION

Background and rationale

Simple benign tracheal stenosis (SBTS) is a rare condition that results from progressive inflammatory narrowing of the upper airways. Its pathophysiology remains unclear.[1] Gradually worsening dyspnoea is the hallmark symptom along with stridor in severe SBTS. Treatment options include endoscopic procedures and open surgery with resection of the affected tracheal segment and end-to-end anastomosis.[2-4] Although open surgery is an effective therapeutic option with a recurrence rate of less than 10%,[3-5] it is associated with a 10 to 30% morbidity, mainly including dysphagia, dysphonia and anastomosis dehiscence.[6 7] In addition, it is important to consider that results of open surgery come from few centres of great expertise.[4 8]

Results of endoscopic procedures are variable with reported success rates ranging from 40 to 90%.[2 4 9 10] Despite their lower success rates than open surgery, endoscopic techniques are generally preferred as first-line therapy, as patients with a recurrence can still be referred for surgery and patients without recurrence will avoid the morbidity associated with surgery.[2 4 9 10]

The main therapeutic endoscopic procedures include dilation and laser resection.[1] Although dilation is the most commonly used technique, observational studies have suggested that endoscopic laser resection may be more effective in preventing recurrence of SBTS. [4] However, current knowledge on endoscopic procedures is mainly based on observational and retrospective studies in which techniques used vary considerably.[2 9 11]

Due to the heterogeneity of endoscopic approaches, we propose to conduct the AERATE trial (dilAtion versus laser Endoscopic Resection in subglottic trAcheal sTEnosis) comparing dilation and endoscopic laser resection for simple benign subglottic tracheal stenosis.

We hypothesize that the success rate of endoscopic laser resection differs from dilation in preventing recurrence of SBTS.

Objective

The overall objective of the present study is to compare the efficacy of endoscopic laser resection and dilation in the treatment of SBTS. The primary endpoint is the recurrence rate of symptomatic SBTS at 2 years. Several secondary endpoints (see below) will also be evaluated (table 1).

Trial design

AERATE is a prospective, multicentre, investigator-initiated study. It is a randomized, controlled, single-blinded, 1:1 parallel-group trial.

METHODS AND ANALYSIS

Study setting

The study will be conducted in three university-affiliated hospitals in France (Toulouse, Grenoble and Marseille) and one in Canada (Québec) with other centres from France and Canada expected to join. All are academic centres that are tertiary referral centres for SBTS and thus have significant experience treating this rare condition. Nearly all patients with SBTS are ultimately referred for care and cluster at such high-volume centres allowing us to anticipate enrolling a representative patient cohort. Each research site has appropriate technological infrastructure for data collection.

Eligibility criteria

We will include patients with simple (*i.e.* length of stenosis < 1cm without underlying cartilage damage)[12], benign subglottic tracheal stenosis referred for endoscopic treatment (first treatment or recurrence) after evaluation by an interventional endoscopist (figure 1). Exclusion criteria

include history of a clinically diagnosed vasculitis (ex: granulomatosis with polyangitis), pregnancy, inability to give informed consent and age under 18 years old (figure 1).

Assignment of interventions

Once consented and enrolled, participants will be randomized (1:1) to receive dilation or laser resection utilizing a clinical electronic data capture (EDC) software (REDCap). The randomization will be stratified on the type of stenosis (first treatment vs recurrence, idiopathic vs other type) and the centre. Stratification, which normalizes the impact of type of SBTS on patient outcomes, has no impact on the statistical power of the trial. The patient will be blinded to the type of endoscopic treatment received.

Interventions

Each patient will perform spirometry and complete questionnaires before performing the endoscopic procedure. Details of these examinations and questionnaires are available in the data collection section. The inclusion visit and the endoscopic procedure can be carried out on the same day.

The endoscopic procedure will be performed under general anaesthesia by an interventional bronchoscopist. Performance of procedures will be limited to 2 bronchoscopists per center with experience in both procedures. Additional anaesthesia of the respiratory tract may be performed by local instillation of lidocaine. Ventilation during the procedure will be carried out by a laryngeal mask or a rigid bronchoscope.

In the endoscopic laser resection arm, a CO_2 or diode (IntermedicTM, Surgical 120, Barcelona, Spain) or similar wavelength laser will be used. The diode laser has an operational wavelength of 808 nm. This laser resection technique is already used and described in benign tracheal stenosis.[4 13-16] Its tissue absorption is higher than the Nd: YAG laser, the coagulation effect is

similar to that of the argon laser, and the tissue vaporization is similar to that of the CO2 laser.[13 16] Power outputs of 40 to 80 watts with pulses of 2 to 6 milliseconds will be used to obtained the desired effect on the stenosis. Triangular portions of the stenosis will be delimitated by laser vaporisation and subsequently resected mechanically or vaporized. Multiple triangles with their tip at the depth of the underlying normal tracheal mucosa will allow us to obtain a residual stenosis of less than 20% while minimizing thermal trauma to underlying tissues (figure 2). No triangle will have its tip on the posterior membrane of the trachea and laser will not the applied circumferentially. If a residual stenosis of less than 20% cannot be obtained, rescue dilatation is allowed but will be reported.

In the dilation arm, a pulmonary dilation balloon (Merit MedicalTM, Elation, Jordan, United States or Boston ScientificTM, CRE, Natick, United States or other similar product) will be inserted in a flexible or rigid bronchoscope and gradually inflated to a diameter corresponding to the diameter of the patient's non-stenotic trachea.[4 17] The balloon will be held at the target diameter for at least 10 seconds. The dilation can be repeated up to 3 times to obtain the desired result. The operator may also alternatively proceed with sequential dilation using a rigid tracheoscope or bronchoscope up to the diameter of the patient's non-stenotic trachea. One radial mechanical incision can be made before dilating the stenosis with an endoscopic scissor or similar mechanical device. The choice of technique will be left to the discretion of the operator and will be reported.

Patients in both groups will receive 4 mg of intravenous dexamethasone during the procedure and 2 mg bid for 48 hours after the procedure. No patient will have endoscopic drug therapy during the procedure (*i.e.* intralesional corticosteroids, mitomycin or others) or have an endobronchial stent placed. Patients not taking a proton pump inhibitor at the time of the screening visit will be prescribed this medication and those taking this medication will continue it. All patients will continue proton pump inhibitor at least until the first recurrence of the

tracheal stenosis or until 2 years if there is no recurrence. Continuation beyond this period will be at the discretion of the treating team. In the presence of side effects attributed by the attending physician to this medication, it may be stopped and its discontinuation must be reported. Proton pump inhibitor is generally very well tolerated and has shown a potentially protective effect against the recurrence of SBTS.[10] No other medication (long-term trimethoprim-sulfamethoxazole, oral corticosteroids) aimed at preventing restenosis will allowed in the current study. If such medication is started for another condition, this should be reported.

Outcomes

The primary outcome is the recurrence rate of subglottic tracheal stenosis at 2 years. We defined recurrence as having a new onset of symptoms along with SBTS of more than 40% (confirmed by endoscopy) requiring a new procedure. Endoscopies will be recorded and sent for central review to confirm the degree of stenosis.

Subgroup analyses will be performed for the primary outcome by stenosis etiology (idiopathic vs other), number of previous endoscopic procedures (first procedure vs second or more) and type of endoscopic procedure (balloon vs rigid dilatation) .

Secondary outcomes include time to first recurrence of SBTS, recurrence rate of SBTS at 1 year, impact on dyspnoea (mMRC, visual analogue scale (VAS), clinical COPD questionnaire)[18], dysphonia (VHI-10)[19] and quality of life (SF-12)[20] of both procedures, measurement of stenosis by cephalo-caudal length at endoscopic follow-up at 1 and 2 year, rate of surgical resection following symptomatic recurrence; depth, length and density of fibrotic reaction in the surgical resection specimen in patients undergoing surgical resection, total number of recurrences over 2 years, rate and type of complications and adverse effects depending on the procedure

Participant timeline

Patients will attend a follow-up visit at 1, 6, 12, 18 and 24 months after the endoscopic procedure. At each visit, a clinical examination, questionnaires and spirometry will be performed. There will be an optional endoscopic follow-up at 12 and 24 months at the discretion of the treating physician and the patient. In addition to scheduled visits, patients will be seen by their treating physician if they present symptoms suggestive of SBTS recurrence. Planned follow up with questionnaires and testing of patients in the study will be stopped when the primary endpoint is met but all patients will attempt a final visit at 24 months to assess total number of recurrences, occurrence of surgical resection of stenosis and undergo bronchoscopy if they consent.

AERATE's enrolment, intervention and follow up schedule is shown in figure 3.

Sample size

For the primary endpoint, we calculated a sample size of 48 patients per arm assuming a 10% recurrence rate in the laser resection arm, 33% in the dilation arm and a two-sided hypothesis with a statistical significance level of 5% and 80% power using R version 4.0.3 and RStudio version 1.4.1103 (R Foundation for Statistical Computing, Vienna, Austria). The assumed recurrence rate of dilation and laser resection at 2 years were based on rates reported in the North American Airway Collaborative (NoAAC) PR02 study.[4] A total sample size of 100 patients (50 per arm) is therefore planned.

Recruitment

The participation of 4 to 10 centres is planned with an annual recruitment of 5 to 10 patients per centre over a recruitment period of 2 to 5 years.

Data collection and management

Data collection for the proposed clinical trial will include the following case report forms (CRFs), implemented in an electronic data capture (EDC) system (REDCap):

- *Baseline:* At initial patient presentation, baseline data collected will include demographics, relevant medical and surgical history and specific history regarding SBTS.

- *Patient-reported outcomes (PROs):* Five validated PRO instruments will be used to assess patient's symptoms. These relate to voice (VHI-10), breathing (clinical COPD questionnaire, mMRC scale and EVA scale) and general QOL (SF-12). Patients will be asked to complete PROs at baseline. In addition, PROs will be repeated at routine intervals post-procedure during the follow-up visits (at 6, 12, 18, 24 months). For patients unable to attempt visit, completion of PROs will be via mailed paper forms or over the phone with an investigator.

- Spirometry: a spirometry will be performed at baseline and during the follow-visits in accordance with recommended techniques [21]

- *Procedure:* Details of the endoscopic procedure will be captured in details; data elements will include date of procedure, operator who performed the procedure, operative findings (eg, type, length and degree of narrowing within the trachea), detailed endoscopic procedure and complications.

- *Recurrence:* At patient recurrence, a subset of features captured at baseline will be captured again; in addition, the characteristics of SBTS by endoscopic evaluation and the details of the repeat procedure will be reported.

The trial will be monitored centrally by the coordinating centre, the Institut Universitaire de Cardiologie et Pneumologie de Quebec. Data entry will be monitored continuously on REDCap, checking for timely data entry, missing data or suspected faulty data.

Statistical analysis

Primary and secondary endpoint analyses will be performed by intention to treat for all randomized patients. In addition, subgroup analyses will be performed for the primary and secondary outcomes by type of stenosis (idiopathic vs other, first procedure vs second or more).

The statistical test for the primary endpoint will be based on a Chi-2 test comparing the recurrence rate between the dilation group and the laser resection group.

For the secondary endpoints, comparisons between groups will be performed with Chi-2 test for categorical data and with a Student test for quantitative data. In addition, analysis of time to recurrence will be based on a log-rank test, comparing the survival distribution of the time-to-first event for the recurrence.

All reported P values will be two sided, with a significance level set at $P < 0.05$.

Statistical analysis will be performed with R version 4.0.3 and RStudio version 1.4.1103 (R Foundation for Statistical Computing, Vienna, Austria)

Data monitoring

Monthly follow ups will be made with all participating sites to ensure all patients are followed as specified in the protocol and that data is entered appropriately.

Harms

Dilation and endoscopic laser resection are two safe and commonly used techniques in interventional bronchoscopy.[13 15] Complications are rare and mostly include transient hypoxia during the procedure. Furthermore, tracheal perforation is a theoretical complication of endoscopic laser resection, but has never been reported to date.

Vital signs will be monitored throughout the procedure according to the local protocol in the interventional bronchoscopy room and an interventional endoscopist will be present.

The adverse events expected in this study are those known and related to all endoscopic procedure [22] (rare, or even exceptional when the contraindications set out in the protocol are respected), that are:

- desaturation> 90% of > 10 seconds
- intra-oral, nasal or endobronchial bleeding
- labial or dental injury
- bronchial laceration
- pneumothorax / pneumomediastinum
- laryngeal edema
- tissue desquamation causing bronchial plug
- pneumonia

All adverse events will be documented and reported according to Canadian and European Union legislation.

Ethics and dissemination

The study is registered on clinical-trials.gov (NCT04719845) and the protocol has site ethics committee and Institutional Review Board (IRB) approval (IUCPQ 22016) in Canada and will obtain ethics approval for France through a delegation of promotion to the participating center in Toulouse. All patients will provide written informed consent using a form reviewed and approved by the IRB. In addition, the study will be conducted in accordance with Good Clinical Practice guidelines and all applicable country, state, and local regulations.

Results of the study, whether completed or not, will be analysed and made available through publication. De-identified individual patient data collected during the trial will be made available for an unlimited time period following publication of trial results.

Trial registration: ClinicalTrials.gov: NCT04719845

Authors contributions

All authors made substantial contributions to the conception and design of the work.

TS and MF wrote the first draft of the manuscript. NG, IA and HD revised the manuscript for important intellectual content. All authors approved the manuscript.

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Competing interest statement: The authors have no conflict of interest to declare.

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Table 1. Outcomes

Primary outcome
- recurrence rate of subglottic tracheal stenosis at 2 years. *Recurrence is defined as having a new onset of symptoms along with SBTS of more than 40% (confirmed by endoscopy) requiring a new procedure.*
Secondary outcomes
- time to first recurrence of SBTS
- recurrence rate of SBTS at 1 year
- impact on dyspnoea (mMRC, visual analogue scale (VAS), clinical COPD questionnaire), dysphonia (VHI-10) and quality of life (SF-12)
- measurement of stenosis by cephalo-caudal length at endoscopic follow-up at 1 and 2 year
- rate of surgical resection following symptomatic recurrence
- total number of recurrences over 2 years
- rate and type of complications and adverse effects
- depth, length and density of fibrotic reaction in the surgical resection specimen in patients undergoing surgical resection

Figure legends

Figure 1. Summary inclusion/exclusion criteria and study design

Figure 2. Proposed technique for laser resection.

Triangular portions of the stenosis will be delimitated by laser vaporisation and subsequently resected mechanically or vaporized. Multiple triangles with their tip at the depth of the underlying normal tracheal mucosa will allow us to obtain a residual stenosis of less than 20% while minimizing thermal trauma to underlying tissues. No triangle will have its tip on the posterior membrane of the trachea and laser will not the applied circumferentially.

Figure 3. AERATE's enrolment, intervention and follow up schedule. * endoscopic evaluation is optional.

Abbreviations: PROs: Patient-reported outcomes, mMRC: modified medical research council, VAS: visual analogue scale, CCQ: clinical COPD questionnaire, VHI: voice handicap index, SF: short form survey.

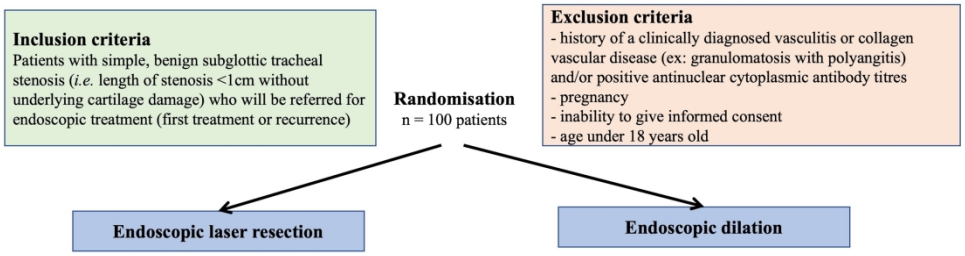

Figure 1

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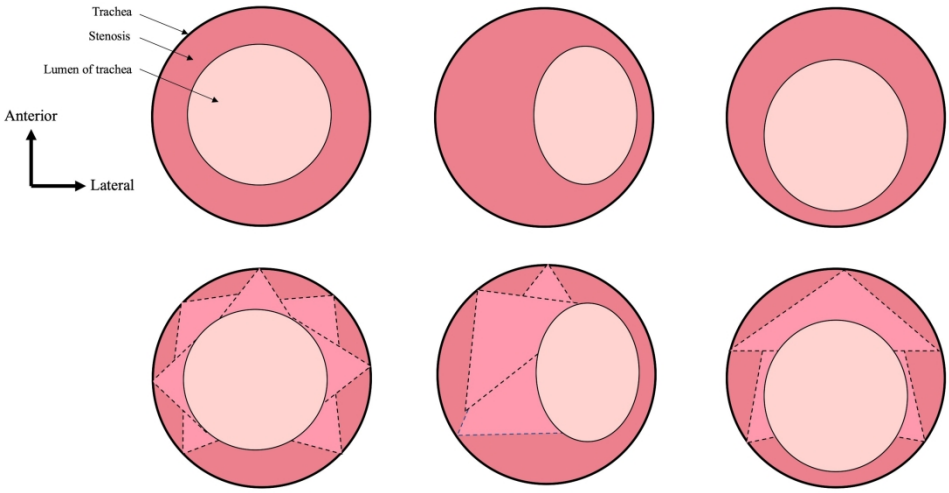
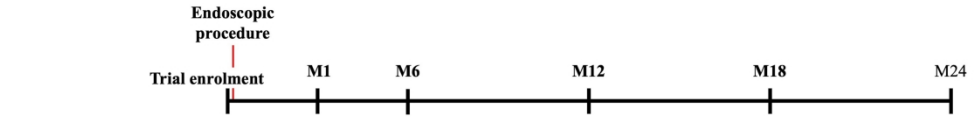


Figure 2

338x190mm (300 x 300 DPI)



Physical examination	x		x	x	x		x	x
PROs (mMRC, CCQ, VAS dyspnea, VIH-10, SF-12)	x		x	x	x		x	x
Spirometry	x		x	x	x		x	x
Bronchoscopy*					(x)			(x)

Figure 3

331x100mm (300 x 300 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	2
Funding	#4	Sources and types of financial, material, and other support	13
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	NA
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	NA
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	NA
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will	5-6

		perform the interventions (eg, surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	6,7,8
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	6,7,8
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6,7,8
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	9
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10

Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	10
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11

Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	NA
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	12
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	1212
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	12-13
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	NA
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	12
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	12

Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	NA
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	NA
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	NA
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	NA
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

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Dilation versus laser resection in subglottic stenosis: protocol for a prospective international multicentre randomized controlled trial (AERATE trial)

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Dilation versus laser resection in subglottic stenosis:

protocol for a prospective international multicentre randomized controlled trial (AERATE trial)

Thibaud Soumagne[1], Nicolas Guibert[2], Ihab Atallah[3], Yves Lacasse[1], Hervé Dutau[4], Marc Fortin[1]

[1] Service de pneumologie, Institut universitaire de cardiologie et de pneumologie de Québec et Université Laval, Québec, Canada

[2] Service de pneumologie, Hôpital Larrey, Université Paul-Sabatier, Centre Hospitalier Universitaire de Toulouse, Toulouse, France.

[3] Clinique universitaire d'ORL, Centre Hospitalier Universitaire Grenoble-Alpes, Grenoble, France

[4] Service d'oncologie thoracique, maladie de la plèvre et pneumologie interventionnelle, hôpital Nord, Assistance publique-hôpitaux de Marseille, Marseille, France.

Corresponding author:

Thibaud Soumagne, MD, PhD

Service de pneumologie, Institut universitaire de cardiologie et de pneumologie de Québec et Université Laval, Québec, Canada

Email: thibaud_soumagne@live.fr

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ABTRACT

Introduction: Subglottic stenosis (SGS) is a rare condition that results from progressive narrowing of the upper airways. Outcomes and treatment options depend on the benign or complex nature of the stenosis. Treatment options for SGS include surgery and endoscopic techniques. The main endoscopic techniques used are dilation and laser resection. Observational and retrospective studies suggest that endoscopic laser resection may be more effective than dilation. We therefore aimed to compare the effectiveness of dilation and laser resection in preventing recurrence of SGS.

Methods and analysis: AERATE is a multicentre, investigator-initiated, randomised controlled trial, comparing endoscopic dilation to endoscopic laser resection for simple benign SGS (less than 1cm long without underlying cartilaginous damage) referred for endoscopic treatment (first treatment or recurrence). The study will be conducted in 3 centres in France and one in Canada with other centres from France and Canada expected to join. The primary outcome is the recurrence rate of stenosis at 2 years. Recurrence is defined as having a new onset of symptoms along with a stenosis of more than 40% (confirmed by bronchoscopy) requiring a new procedure. A sample size of 100 patients is calculated for the primary endpoint assuming a 10% recurrence rate in the laser resection group and 33% in the dilation group with a statistical significance level of 5%, a power of 80%.

Ethics and dissemination: This study is approved by local and national ethics committees as required. Results will be published, and trial data will be made available.

Trial registration: ClinicalTrials.gov: NCT04719845

Keywords: subglottic stenosis, tracheal stenosis, dilation, laser resection, recurrence

Strengths and limitations of this study

- This is the first randomized controlled trial comparing endoscopic procedures in SGS and is in fact the first randomized controlled trial in the field of SGS to our knowledge.

- The primary endpoint is symptomatic endoscopically confirmed recurrence rate at 2 years which is an objective clinical endpoint. This outcome will allow us to provide a definitive answer to an important clinical question: "What is the most effective endoscopic technique to treat SGS?"

- Adequate statistical power however relies on sufficient recruitment which can be a challenge in rare disease.

INTRODUCTION

Background and rationale

Simple benign subglottic stenosis (SGS) is a rare condition that results from progressive inflammatory narrowing of the upper airways. Its pathophysiology remains unclear.[1] Gradually worsening dyspnoea is the hallmark symptom along with stridor in severe SGS. Treatment options include endoscopic procedures and open surgery with resection of the affected tracheal segment and end-to-end anastomosis.[2-4] Although open surgery is an effective therapeutic option with a recurrence rate of less than 10%,[3-5] it is associated with a 10 to 30% morbidity, mainly including dysphagia, dysphonia and anastomosis dehiscence.[6 7] In addition, it is important to consider that results of open surgery come from few centres of great expertise.[4 8]

Results of endoscopic procedures are variable with reported success rates ranging from 40 to 90%.[2 4 9 10] Despite their lower success rates than open surgery, endoscopic techniques are generally preferred as first-line therapy, as patients with a recurrence can still be referred for surgery and patients without recurrence will avoid the morbidity associated with surgery.[2 4 9 10]

The main therapeutic endoscopic procedures include dilation and laser resection.[1] Although dilation is the most commonly used technique, observational studies have suggested that endoscopic laser resection may be more effective in preventing recurrence of SGS. [4] However, current knowledge on endoscopic procedures is mainly based on observational and retrospective studies in which techniques used vary considerably.[2 9 11]

Due to the heterogeneity of endoscopic approaches, we propose to conduct the AERATE trial (dilAtion versus laser Endoscopic Resection in subglottic trAcheal sTEnosis) comparing dilation and endoscopic laser resection for simple benign subglottic stenosis.

We hypothesize that the success rate of endoscopic laser resection differs from dilation in preventing recurrence of SGS.

Objective

The overall objective of the present study is to compare the efficacy of endoscopic laser resection and dilation in the treatment of SGS. The primary endpoint is the recurrence rate of symptomatic SGS at 2 years. Several secondary endpoints (see below) will also be evaluated (table 1).

Trial design

AERATE is a prospective, multicentre, investigator-initiated study. It is a randomized, controlled, single-blinded, 1:1 parallel-group trial.

METHODS AND ANALYSIS

Study setting

The study will be conducted in three university-affiliated hospitals in France (Toulouse, Grenoble and Marseille) and one in Canada (Québec) with other centres from France and Canada expected to join. All are academic centres that are tertiary referral centres for SGS and thus have significant experience treating this rare condition. Nearly all patients with SGS are ultimately referred for care and cluster at such high-volume centres allowing us to anticipate enrolling a representative patient cohort. Each research site has appropriate infrastructure for study setting.

Eligibility criteria

We will include patients with simple (*i.e.* length of stenosis < 1cm without underlying cartilage damage)[12] benign subglottic stenosis referred for endoscopic treatment (first treatment or recurrence) after evaluation by an interventional bronchoscopist (figure 1). Exclusion criteria

include history of a clinically diagnosed vasculitis (ex: granulomatosis with polyangitis), pregnancy, inability to give informed consent and age under 18 years old (figure 1).

Assignment of interventions

Once consented and enrolled, participants will be randomized (1:1) to receive dilation or laser resection utilizing a clinical electronic data capture (EDC) software (REDCap). The randomization will be stratified on the type of stenosis (first treatment vs recurrence, idiopathic vs other type) and the centre. Stratification, which normalizes the impact of type of SGS on patient outcomes, has no impact on the statistical power of the trial. The patient will be blinded to the type of endoscopic treatment received.

Interventions

Each patient will perform spirometry and complete questionnaires before performing the endoscopic procedure. Details of these examinations and questionnaires are available in the data collection section. The inclusion visit and the endoscopic procedure can be carried out on the same day.

The endoscopic procedure will be performed under general anaesthesia by an interventional bronchoscopist. Performance of procedures will be limited to 2 bronchoscopists per center with experience in both procedures. Additional anaesthesia of the respiratory tract may be performed by local instillation of lidocaine. Ventilation during the procedure will be carried out by a laryngeal mask or a rigid bronchoscope.

In the endoscopic laser resection arm, a CO_2 or diode (IntermedicTM, Surgical 120, Barcelona, Spain) or similar wavelength laser will be used. The diode laser has an operational wavelength of 808 nm. This laser resection technique is already used and described in SGS.[4 13-16] Its tissue absorption is higher than the Nd: YAG laser, the coagulation effect is similar to that of the

argon laser, and the tissue vaporization is similar to that of the CO2 laser.[13 16] Power outputs starting from 5 watts and up to 40 watts with pulses of 200 to 400 milliseconds and pauses of 200 milliseconds will be used to obtain the desired effect on the stenosis. Triangular portions of the stenosis will be delimitated by laser vaporisation and subsequently resected mechanically or vaporized. Multiple triangles with their tip at the depth of the underlying normal tracheal mucosa will allow us to obtain a residual stenosis of less than 20% while minimizing thermal trauma to underlying tissues (figure 2). No triangle will have its tip on the posterior membrane of the trachea and laser will not the applied circumferentially. If a residual stenosis of less than 20% cannot be obtained, rescue dilatation is allowed but will be reported.

In the dilation arm, a pulmonary dilation balloon (Merit MedicalTM, Elation, Jordan, United States or Boston ScientificTM, CRE, Natick, United States or other similar product) will be inserted in a flexible or rigid bronchoscope and gradually inflated to a diameter corresponding to the diameter of the patient's non-stenotic trachea.[4 17] The balloon will be held at the target diameter for at least 10 seconds. The dilation can be repeated up to 3 times to obtain the desired result. The operator may also alternatively proceed with sequential dilation using a rigid tracheoscope or bronchoscope up to the diameter of the patient's non-stenotic trachea. One radial mechanical incision can be made before dilating the stenosis with an endoscopic scissor or similar mechanical device. The choice of technique will be left to the discretion of the operator and will be reported.

Patients in both groups will receive 4 mg of intravenous dexamethasone during the procedure and 2 mg bid for 48 hours after the procedure. No patient will have endoscopic drug therapy during the procedure (*i.e.* intralesional corticosteroids, mitomycin or others) or have an endobronchial stent placed.

Proton pump inhibitor (PPI) has shown a potentially protective effect against the recurrence of SGS and is generally very well tolerated.[4 10] The main rationale for PPI treatment is based on data supporting a high prevalence of gastroesophageal reflux disease (GERD) in patients with SGS and the possible impact of GERD on recurrence.[18 19] PPI has however, be mainly reported in combination to laser resection. In studies comparing laser resection in combination to PPI to dilation alone, PPI might be a confusing factor in the evaluation of endoscopic treatment effect (*i.e.* laser resection *versus* dilation).[4] In order to evaluate the effect of the endoscopic technique, we therefore decide to standardize the post-operative intervention in the current study. All patients included in the study will be prescribed PPI at the time of the screening visit and those already taking this medication will continue it. All patients will continue PPI at least until the first recurrence of the subglottic stenosis or until 2 years if there is no recurrence. Continuation beyond this period will be at the discretion of the treating team. In the presence of side effects attributed by the attending physician to this medication, it may be stopped and its discontinuation must be reported.

No other medication (long-term trimethoprim-sulfamethoxazole, oral corticosteroids) aimed at preventing restenosis will allowed in the current study. If such medication is started for another condition, this would be reported.

Outcomes

The primary outcome is the recurrence rate of subglottic stenosis at 2 years. We defined recurrence as having a new onset of symptoms along with SGS of more than 40% (confirmed by bronchoscopy) requiring a new procedure. Endoscopies will be recorded and sent for central blinded review to confirm the degree of stenosis.

Subgroup analyses will be performed for the primary outcome by stenosis etiology (idiopathic vs other), number of previous endoscopic procedures (first procedure vs second or more) and type of endoscopic procedure (balloon vs rigid dilatation).

Secondary outcomes include time to first recurrence of SGS, recurrence rate of SGS at 1 year, impact on dyspnoea (mMRC, visual analogue scale (VAS), clinical COPD questionnaire)[20], dysphonia (VHI-10)[21] and quality of life (SF-12)[22] of both procedures, measurement of stenosis by cephalo-caudal length at endoscopic follow-up at 1 and 2 year, rate of surgical resection following symptomatic recurrence; depth, length and density of fibrotic reaction in the surgical resection specimen in patients undergoing surgical resection, total number of recurrences over 2 years, rate and type of complications and adverse effects depending on the procedure

Participant timeline

Patients will attend a follow-up visit at 1, 6, 12, 18 and 24 months after the endoscopic procedure. At each visit, a clinical examination, questionnaires and spirometry will be performed. There will be an optional endoscopic follow-up at 12 and 24 months at the discretion of the treating physician and the patient. In addition to scheduled visits, patients will be seen by their treating physician if they present symptoms suggestive of SGS recurrence. Planned follow up with questionnaires and testing of patients in the study will be stopped when the primary endpoint is met but all patients will attempt a final visit at 24 months to assess total number of recurrences, occurrence of surgical resection of stenosis and undergo bronchoscopy if they consent.

AERATE's enrolment, intervention and follow up schedule is shown in figure 3.

Sample size

For the primary endpoint, we calculated a sample size of 48 patients per arm assuming a 10% recurrence rate in the laser resection arm, 33% in the dilation arm and a two-sided hypothesis with a statistical significance level of 5% and 80% power using R version 4.0.3 and RStudio version 1.4.1103 (R Foundation for Statistical Computing, Vienna, Austria). The assumed recurrence rate of dilation and laser resection at 2 years were based on rates reported in the North American Airway Collaborative (NoAAC) PR02 study.[4] A total sample size of 100 patients (50 per arm) is therefore planned.

Recruitment

The participation of 4 to 10 centres is planned with an annual recruitment of 5 to 10 patients per centre over a recruitment period of 2 to 5 years.

Data collection and management

Data collection for the proposed clinical trial will include the following case report forms (CRFs), implemented in an electronic data capture (EDC) system (REDCap):

- *Baseline:* At initial patient presentation, baseline data collected will include demographics, relevant medical and surgical history and specific history regarding SGS.

- *Patient-reported outcomes (PROs):* Five validated PRO instruments will be used to assess patient's symptoms. These relate to voice (VHI-10),[21] breathing (clinical COPD questionnaire, mMRC scale and EVA scale)[20] and general QOL (SF-12).[22] Patients will be asked to complete PROs at baseline. In addition, PROs will be repeated at routine intervals post-procedure during the follow-up visits (at 6, 12, 18, 24 months). For patients unable to attempt visit, completion of PROs will be via mailed paper forms or over the phone with an investigator.

- Spirometry: a spirometry will be performed at baseline and during the follow-visits in accordance with recommended techniques [23]

- *Procedure:* Details of the endoscopic procedure will be captured in details; data elements will include date of procedure, operator who performed the procedure, operative findings (eg, type, length and degree of narrowing within the trachea), detailed endoscopic procedure and complications.

- *Recurrence:* At patient recurrence, a subset of features captured at baseline will be captured again; in addition, the characteristics of SGS by endoscopic evaluation and the details of the repeat procedure will be reported.

The trial will be monitored centrally by the coordinating centre, the Institut Universitaire de Cardiologie et Pneumologie de Quebec. Data entry will be monitored continuously on REDCap, checking for timely data entry, missing data or suspected faulty data.

Statistical analysis

Primary and secondary endpoint analyses will be performed by intention to treat for all randomized patients. In addition, subgroup analyses will be performed for the primary and secondary outcomes by type of stenosis (idiopathic vs other, first procedure vs second or more).

The statistical test for the primary endpoint will be based on a Chi-2 test comparing the recurrence rate between the dilation group and the laser resection group.

For the secondary endpoints, comparisons between groups will be performed with Chi-2 test for categorical data and with a Student test for quantitative data. In addition, analysis of time to recurrence will be based on a log-rank test, comparing the survival distribution of the time-to-first event for the recurrence.

Multivariate logistic regression analysis will be performed to evaluate factor influencing recurrence.

All reported P values will be two sided, with a significance level set at $P < 0.05$.

Statistical analysis will be performed with R version 4.0.3 and RStudio version 1.4.1103 (R Foundation for Statistical Computing, Vienna, Austria)

Data monitoring

Monthly follow ups will be made with all participating sites to ensure all patients are followed as specified in the protocol and that data is entered appropriately.

Harms

Dilation and endoscopic laser resection are two safe and commonly used techniques in interventional bronchoscopy.[13 15] Complications are rare and mostly include transient hypoxia during the procedure. Furthermore, tracheal perforation is a theoretical complication of endoscopic laser resection, but has never been reported to date.

Vital signs will be monitored throughout the procedure according to the local protocol in the interventional bronchoscopy room and an interventional bronchoscopist will be present.

The adverse events expected in this study are those known and related to all endoscopic procedure [24] (rare, or even exceptional when the contraindications set out in the protocol are respected), that are:

- desaturation> 90% of > 10 seconds
- intra-oral, nasal or endobronchial bleeding
- labial or dental injury
- bronchial laceration
- pneumothorax / pneumomediastinum

- laryngeal oedema
- tissue desquamation causing bronchial plug
- pneumonia

All adverse events will be documented and reported according to Canadian and European Union legislation.

Ethics and dissemination

The study is registered on clinical-trials.gov (NCT04719845) and the protocol has site ethics committee and Institutional Review Board (IRB) approval (IUCPQ 22016). All patients will provide written informed consent using a form reviewed and approved by the IRB (online supplemental). In addition, the study will be conducted in accordance with Good Clinical Practice guidelines and all applicable country, state, and local regulations.

Results of the study, whether completed or not, will be analysed and made available through publication. De-identified individual patient data collected during the trial will be made available for an unlimited time period following publication of trial results.

Patient and public involvement

Subglottic stenosis is a rare condition without evidence of a therapeutic option with a high standard of proof. Endoscopic techniques are the most used treatment options including dilation and laser resection. Current knowledge on these two procedures is mainly based on observational studies. These techniques have not been compared yet in a randomized trial. The AERATE trial will therefore help to determine to best endoscopic option in patients with SGS.

Patients and public were not involved in the study design or conduct, or reporting, or dissemination plans of this research. Participants will have access to the findings of the study on request.

Trial registration: ClinicalTrials.gov: NCT04719845

Authors contributions

TS, NG, IA, YL, HD and MF conceived the study. TS and MF initially designed the study. NG, IA, HD and MF elaborated the laser intervention. TS, YL and MF elaborated the statistical design of the study. TS and MF wrote the first manuscript draft. All authors made critical revisions and approved the final manuscript.

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Competing interest statement: The authors have no conflict of interest to declare.

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Table 1. Outcomes

Primary outcome
- recurrence rate of subglottic stenosis at 2 years. *Recurrence is defined as having a new onset of symptoms along with SGS of more than 40% (confirmed by bronchoscopy) requiring a new procedure.*
Secondary outcomes
- time to first recurrence of SGS
- recurrence rate of SGS at 1 year
- impact on dyspnoea (mMRC, visual analogue scale (VAS), clinical COPD questionnaire), dysphonia (VHI-10) and quality of life (SF-12)
- measurement of stenosis by cephalo-caudal length at endoscopic follow-up at 1 and 2 year
- rate of surgical resection following symptomatic recurrence
- total number of recurrences over 2 years
- rate and type of complications and adverse effects
- depth, length and density of fibrotic reaction in the surgical resection specimen in patients undergoing surgical resection

Figure legends

Figure 1. Summary inclusion/exclusion criteria and study design

Figure 2. Proposed technique for laser resection.

Triangular portions of the stenosis will be delimitated by laser vaporisation and subsequently resected mechanically or vaporized. Multiple triangles with their tip at the depth of the underlying normal tracheal mucosa will allow us to obtain a residual stenosis of less than 20% while minimizing thermal trauma to underlying tissues. No triangle will have its tip on the posterior membrane of the trachea and laser will not the applied circumferentially.

Figure 3. AERATE's enrolment, intervention and follow up schedule. * endoscopic evaluation is optional.

Abbreviations: PROs: Patient-reported outcomes, mMRC: modified medical research council, VAS: visual analogue scale, CCQ: clinical COPD questionnaire, VHI: voice handicap index, SF: short form survey.

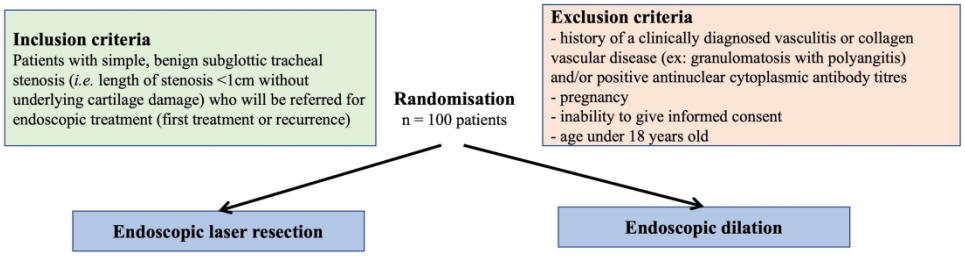

Figure 1

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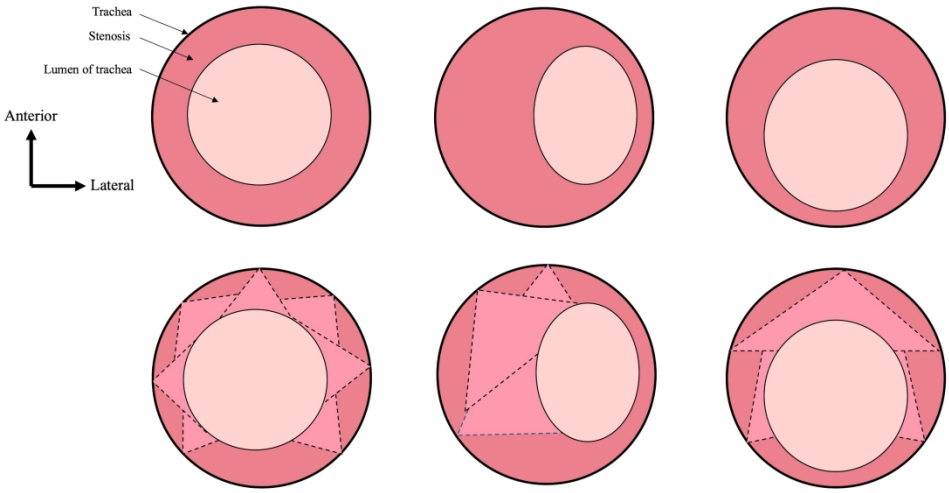

Figure 2

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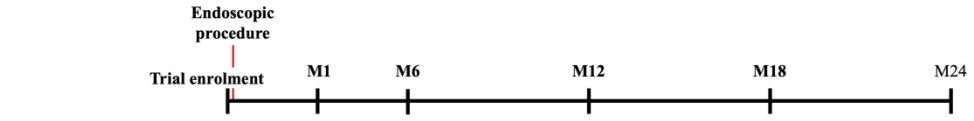

Physical examination	x		x	x	x		x	x
PROs (mMRC, CCQ, VAS dyspnea, VIH-10, SF-12)	x		x	x	x		x	x
Spirometry	x		x	x	x		x	x
Bronchoscopy*					(x)			(x)

Figure 3

331x100mm (600 x 600 DPI)

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DT4617

Nom du participant: _____

Date de version: _____

Date d'approbation: _____

Signature:

FORMULAIRE D'INFORMATION ET DE CONSENTEMENT

Titre du projet : **Résection endoscopique par laser versus dilatation dans la prise en charge de la sténose trachéale : essai randomisé multicentrique**

Chercheur responsable : Marc Fortin, MD

Cochercheur : Thibaud Soumage, MD, PhD

Collaborateur : Hervé Dutau, MD; Nicolas Guibert, MD, PhD

Financement : **Fonds académique de pneumologie interventionnelle de l'IUCPQ-UL**

Nous sollicitons votre participation à un projet de recherche. Cependant, avant d'accepter de participer à ce projet et de signer ce formulaire d'information et de consentement, veuillez prendre le temps de lire, de comprendre et de considérer attentivement les renseignements qui suivent.

Ce formulaire peut contenir des mots que vous ne comprenez pas. Nous vous invitons à poser toutes les questions que vous jugerez utiles au chercheur responsable du projet ou aux autres membres du personnel affecté au projet de recherche et à leur demander de vous expliquer tout mot ou renseignement qui n'est pas clair.

INTRODUCTION

Vous êtes invité(e) à participer à cette étude en recherche clinique car vous avez une sténose (rétrécissement) de la trachée et votre pneumologue vous a proposé une intervention pour ouvrir cette sténose et redonner à votre trachée une taille normale afin de vous permettre de respirer plus facilement. Il existe plusieurs façons de faire cette intervention, mais nous ignorons encore laquelle est la plus efficace. On peut dilater (ouvrir) la sténose en y gonflant un ballon ou en y passant des tubes de tailles progressivement plus importantes ou on peut brûler la sténose avec un laser. Malheureusement, chez certains patients, la sténose revient dans les années qui suivent l'intervention.

BUT DE L'ÉTUDE

Dans cette étude, nous voulons déterminer la fréquence de récidive symptomatique de la sténose trachéale chez les participants ayant eu une dilatation trachéale comparativement à ceux ayant eu un traitement au laser. Environ 100 patients participeront à cette étude en France et au Québec, dont au moins 30 patients à l'IUCPQ-UL.

DÉROULEMENT DU PROJET DE RECHERCHE

En participant à ce projet, vous serez attitré au hasard à une des procédures endoscopiques étudiée (dilatation ou traitement au laser). Vous ne serez pas mis au courant du traitement que vous recevrez et seul le médecin effectuant la procédure sera au courant. Il sera toutefois possible à tout moment, si jugé médicalement nécessaire, de le savoir.

La visite de sélection et d'inclusion et la réalisation de la procédure endoscopique pourront s'effectuer sur une seule et même journée.

Avant la procédure, chaque patient réalisera une spirométrie et remplira les questionnaires (mMRC, EVA, VHI-10, SF-12). Si vous ne recevez pas de médication pour l'acidité gastrique (inhibiteur de la pompe à proton) au moment de la visite de sélection vous recevrez une prescription pour cette médication. Si vous en prenez déjà vous poursuivez cette médication. Cette médication sera poursuivie au moins jusqu'à la première récidive de la sténose trachéale. La poursuite au-delà de cette période est à la discrétion de l'équipe traitante. En présence d'effets indésirables attribués par le médecin traitant à cette médication, elle pourra être cessée et son arrêt devra être rapporté. Il s'agit d'une médication généralement très bien tolérée qui a démontré un effet potentiellement protecteur quant à la récidive des sténoses bénignes des voies aériennes. Aucune autre médication pour la prévention de la resténose ne sera débutée.

La procédure endoscopique sera réalisée par un bronchoscopiste interventionnel sous anesthésie générale. Pendant ce temps vous un support ventilatoire sera assuré par un anesthésiste. L'une des deux procédures suivantes choisie au hasard sera effectuée : le traitement au laser de la sténose ou la dilatation de la sténose avec un ballon ou un tube rigide après y avoir fait une coupure,

Vous recevrez une dose de cortisone intraveineuse durant la procédure et prendrez 2 comprimés de cortisone pendant les 2 jours suivant la procédure.

Vous serez revus en consultation un mois après l'intervention, puis à 6 mois et ensuite tous les 6 mois pour 2 ans de suivi total. À la fin des 2 ans, votre suivi se poursuivra comme à l'habitude, mais le projet de recherche sera terminé. À chaque suivi vous serez examiné, vous répondrez à des questionnaires et vous ferez une spirométrie. Lors du test de spirométrie vous aurez à vous mettre un pince-nez, inspirer et expirer avec force dans un embout buccal à plusieurs reprises. Parfois, ces procédures peuvent causer de la toux, une sensation d'oppression, de l'essoufflement ou un léger étourdissement

Examen clinique	x		x	x		x	x	x
Questionnaires (mMRC, COPD dyspnea, VIH-10, EAT-10, SF-12, FoP-Q-SF)	x		x	x		x	x	x
EFR complètes	x		x	x		x	x	x
Endoscopie souple*						(x)		(x)

Une bronchoscopie de contrôle vous sera proposée à 1 et 2 ans après l'intervention ou avant si vous développez des symptômes de récidive de la sténose. Il s'agit d'examens qui sont habituellement faits dans le suivi de votre maladie à l'IUCPQ-UL.

RISQUES ASSOCIÉS AU PROJET DE RECHERCHE

Les risques associés à la dilatation ou le traitement au laser de la sténose trachéale sont les mêmes pour les deux procédures. Si vous décidez de ne pas participer au projet de recherche, il vous est médicalement recommandé de subir une procédure qui vous expose à ces risques. La grande majorité des patients subissant ces interventions n'ont pas d'effets secondaires outre un mal de gorge ou une voix enrouée qui se résout en quelques heures et qui peut durer jusqu'à quelques jours. Les risques plus rares comprennent la baisse du taux d'oxygène dans le sang (hypoxie), le saignement des lèvres, de la bouche, du nez ou des voies aériennes, la blessure dentaire ou d'une lèvre, le bronchospasme, la perforation d'une bronche ou d'un poumon (pneumothorax ou pneumomédiastin), l'enflure de la gorge (œdème laryngé) ou la pneumonie. Il est possible que vous crachiez du sang au cours des 24 heures suivant l'intervention. La quantité est habituellement légère.

La spirométrie peut causer un léger serrement dans la poitrine et de la toux (aggravation des symptômes de l'asthme); ces effets sont temporaires. Un traitement par inhalation d'un bronchodilatateur à action rapide peut être administré si nécessaire pour dilater vos voies respiratoires et vous aider à mieux respirer

L'anesthésie générale bien qu'elle soit habituellement très sécuritaire, présente quelques risques. Les problèmes les plus fréquents associés à l'anesthésie sont une sensation de malaise ou de vomissements, une ecchymose (bleu) au site des injections, un mal de gorge ou une voix enrouée. Ils s'améliorent généralement très rapidement. Les dents pourraient être endommagées, mais cela est rare. Le risque de lésions au cerveau ou de décès en raison de l'anesthésie est très faible.

INCONVÉNIENTS ASSOCIÉS AU PROJET DE RECHERCHE

Un inconvénient associé à votre participation à ce projet de recherche est de devoir remplir des questionnaires supplémentaires lors de vos visites de suivi.

AVANTAGES

Il se peut que vous retiriez un bénéfice personnel de votre participation à ce projet de recherche si vous recevez un traitement qui s'avère plus efficace pour diminuer les risques de récidive de sténose, mais on ne peut vous l'assurer. Par ailleurs, les résultats obtenus contribueront à l'avancement des connaissances dans ce domaine.

PARTICIPATION VOLONTAIRE ET POSSIBILITÉ DE RETRAIT

Votre participation à ce projet de recherche est volontaire. Vous êtes donc libre de refuser d'y participer. Vous pouvez également vous retirer de ce projet à n'importe quel moment, sans avoir à donner de raisons, en informant l'équipe de recherche.

Votre décision de ne pas participer à ce projet de recherche ou de vous en retirer n'aura aucune conséquence sur la qualité des soins et des services auxquels vous avez droit ou sur votre relation avec l'équipe qui les dispensent.

Le chercheur responsable du projet de recherche ou le comité d'éthique de la recherche de l'IUCPQ-UL, peuvent mettre fin à votre participation, sans votre consentement, si de nouvelles découvertes ou informations indiquent que votre participation au projet n'est plus dans votre intérêt, si vous ne respectez pas les consignes du projet de recherche ou s'il existe des raisons administratives d'abandonner le projet.

Si vous vous retirez ou êtes retiré du projet, l'information et le matériel déjà recueillis dans le cadre de ce projet seront néanmoins conservés, analysés ou utilisés pour assurer l'intégrité du projet.

Toute nouvelle connaissance acquise durant le déroulement du projet qui pourrait affecter votre décision de continuer d'y participer vous sera communiquée rapidement.

CONFIDENTIALITÉ

Durant votre participation à ce projet, le chercheur responsable ainsi que son personnel recueilleront et consigneront dans un dossier de recherche les renseignements vous concernant et nécessaires pour répondre aux objectifs scientifiques de ce projet.

Ces renseignements peuvent comprendre les informations contenues dans vos dossiers médicaux concernant votre état de santé passé et présent, vos habitudes de vie ainsi que les résultats de tous les tests, examens et procédures que vous aurez à subir durant ce projet. Votre dossier peut aussi comprendre d'autres renseignements tels que votre nom, votre sexe, votre date de naissance et votre origine ethnique.

Tous les renseignements recueillis demeureront strictement confidentiels dans les limites prévues par la loi. Vous ne serez identifié que par un numéro de code. La clé du code reliant votre nom à votre dossier de recherche sera conservée par le chercheur responsable.

Pour assurer votre sécurité, une copie du formulaire de consentement sera versée dans votre dossier médical. Par conséquent, toute personne ou compagnie à qui vous donnerez accès à votre dossier médical aura accès à ces informations.

Le chercheur responsable du projet utilisera les données à des fins de recherche dans le but de répondre aux objectifs scientifiques du projet décrits dans le formulaire d'information et de consentement. Ces données seront conservées pendant 5 ans par le chercheur responsable.

Les données de recherche pourront être publiées ou faire l'objet de discussions scientifiques, mais il ne sera pas possible de vous identifier.

À des fins de surveillance et de contrôle, de protection, de sécurité votre dossier de recherche ainsi que vos dossiers médicaux pourront être consultés par une personne mandatée de l'établissement, ou du comité d'éthique de la recherche de l'IUCPQ-UL. Ces personnes et ces organismes adhèrent à une politique de confidentialité.

Vous avez le droit de consulter votre dossier de recherche pour vérifier les renseignements recueillis, et les faire rectifier au besoin.

FINANCEMENT DU PROJET DE RECHERCHE

La réalisation de ce projet de recherche sera financée par le fonds local de l'IUCPQ-UL du chercheur : *Fonds académique de pneumologie interventionnelle*.

INDEMNISATION EN CAS DE PRÉJUDICE ET DROITS DU PARTICIPANT DE RECHERCHE

Si vous deviez subir quelque préjudice que ce soit à la suite de toute procédure reliée à ce projet de recherche, vous recevrez tous les soins et services requis par votre état de santé.

En acceptant de participer à ce projet, vous ne renoncez à aucun de vos droits et vous ne libérez pas le chercheur responsable de ce projet de recherche et l'établissement de leur responsabilité civile et professionnelle.

COMPENSATION

Vous ne recevrez pas de compensation financière pour votre participation à ce projet de recherche.

IDENTIFICATION DES PERSONNES-RESSOURCES

Si vous avez des questions ou éprouvez des problèmes en lien avec le projet de recherche, ou si vous souhaitez vous en retirer, vous pouvez communiquer avec le médecin responsable au numéro suivant :

Marc Fortin, MD, pneumologue
Institut universitaire de cardiologie et de pneumologie de Québec - Université Laval
2725, chemin Sainte-Foy
Québec (Québec) G1V 4G5
Téléphone : (418) 656-8711

COMMISSAIRE AUX PLAINTES

Pour toute question concernant vos droits en tant que participant à ce projet de recherche ou si vous avez des plaintes ou des commentaires à formuler, vous pouvez communiquer avec :

La commissaire locale aux plaintes et à la qualité des services
Institut universitaire de cardiologie et de pneumologie de Québec – Université Laval
2725, chemin Sainte-Foy
Québec (Québec) G1V 4G5
Téléphone : 418 656-4945

SURVEILLANCE DES ASPECTS ÉTHIQUES DU PROJET DE RECHERCHE

Le comité d'éthique de la recherche de l'IUCPQ-UL a approuvé ce projet de recherche et en assure le suivi. Une approbation éthique est obligatoire avant le démarrage du projet. De plus, il approuvera au préalable toute révision et toute modification apportée au formulaire d'information et de consentement et au protocole de recherche.

Titre du projet : **Résection endoscopique par laser versus dilatation dans la prise en charge de la sténose trachéale : essai randomisé multicentrique**

FORMULAIRE DE CONSENTEMENT

- J'ai pris connaissance du formulaire d'information et de consentement. On m'a expliqué le projet et le présent formulaire d'information et de consentement. On a répondu à mes questions et on m'a laissé le temps voulu pour prendre une décision. Après réflexion, je consens à participer à ce projet de recherche aux conditions qui y sont énoncées.
- J'autorise l'équipe de recherche à avoir accès à mon dossier médical.
- Une copie signée et datée du présent formulaire d'information et de consentement me sera remise.
- J'autorise le chercheur à informer mon médecin traitant de ma participation à ce projet et à lui transmettre les informations pertinentes si ces informations peuvent avoir une utilité clinique : Oui ☐ Non ☐

Nom et signature du participant de recherche Date

J'ai expliqué au participant de recherche les termes du présent formulaire d'information et de consentement et j'ai répondu aux questions qu'il m'a posées.

Nom et signature de la personne qui obtient le consentement Date

Je certifie qu'on a expliqué au participant de recherche les termes du présent formulaire d'information et de consentement, que l'on a répondu aux questions que le participant de recherche avait à cet égard et qu'on lui a clairement indiqué qu'il demeure libre de mettre un terme à sa participation, et ce, sans préjudice.

Je m'engage, avec l'équipe de recherche, à respecter ce qui a été convenu au formulaire d'information et de consentement et à en remettre une copie signée au participant de recherche.

Nom et signature du chercheur responsable du projet de recherche Date

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	2
Funding	#4	Sources and types of financial, material, and other support	13
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	NA
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	NA
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	NA
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will	5-6

		perform the interventions (eg, surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	6,7,8
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	6,7,8
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6,7,8
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	9
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10

Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	10
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11

Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	NA
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	12
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	1212
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	12-13
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	NA
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	12
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	12

Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	NA
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	NA
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	NA
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	NA
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA